REMARKS

The non-final Office Action dated March 27, 2006 has been reviewed and the following remarks are made in response thereto. In view of the following remarks, Applicants respectfully request reconsideration of this application and timely allowance of the pending claims. Upon entry of the instant amendment, claims 33, 37-51 and 53-74 are pending.

Claims 33, 37-51, 53-57, 62, 64-66, 68, and 70-73, are withdrawn from consideration as being directed to a non-elected invention. Claims 58-61, 63, 67, 69, and 74 are currently under examination.

The Office Action's statement that claim 69 is withdrawn from consideration as being directed to a non-elected invention is an inadvertent error, since claim 69 is currently under examination.

Amendments to the Claims

Claims 58 and 60 have been amended to correct obvious typographical errors. As such, written support for the claim amendments can be found in the original claims and throughout the specification. Accordingly, Applicants submit that no prohibited new matter has been added by way of the claim amendments.

Obviousness-Type Double Patenting Rejections

Claims 58-61, 63, 67, 69 and 74 were provisionally rejected under the judicially created doctrine of non-statutory obviousness-type double patenting as being unpatentable over claims 51-59 of co-pending U.S. Patent Application No. 10/519,193 and claims 1-15 of copending U.S. Patent Application No. 11/018574.

Claims 58-61, 63, 67, 69, and 74 of the present application are directed to a method of modifying an agent to enhance its efficacy comprising associating the agent with one or more cationic components to produce a composition having an optimal zeta potential for targeting to an activated vascular site and dispersing the composition in a medium to form colloids having a size of about 10 nm to about 400 nm, wherein the composition has a zeta potential in the range of about +30 mV to +65 mV in about 0.05 mM KCl solution at about pH 7.5.

Claims 51-59 of U.S. Patent Application 10/519,193 are directed to methods of treating or preventing a disease, a method of producing a nanoaggregate, and a pharmaceutical composition. The claims, directed to methods of treating or preventing a disease or to a pharmaceutical composition, are patentably distinct from the presently claimed invention. Applicants respectfully point out that in the present application, claims 41-50 are withdrawn from examination as being directed to a separate

invention. Regarding the claims directed to a method of producing a nanoaggregate, the claims recite specific steps that are distinct from the steps required by the present method of modifying an agent.

Claims 1-15 of U.S. Patent Application 11/018,574 are directed to methods of producing a liposomal composition containing at least one amphiphile selected from cationic lipids comprising specific steps that are distinct from the steps required by the present method of modifying an agent.

Claim Objections

Claims 58-61, 63, 67, 69 and 74 were objected to for failing to comply with a formality. In particular the Office Action purports that the recitation of pH 75 in claim 58 renders the claim (and claim dependent thereon) ambiguous.

Without acquiescing to the merits of the objection, and solely to expedite prosecution of the pending application, Applicants have amended claim 58 to recite pH 7.5. Therefore, Applicants respectfully request that the rejection of claims 58-61, 63, 67, 69 and 74 be withdrawn.

Rejection Under 35 U.S.C. § 112 (second paragraph)

Claim 61 was rejected under 35 U.S.C. § 112 (second paragraph) as being indefinite. Specifically, the Office Action purports that the term "magnetosome" is not defined in the specification. Applicants respectfully traverse the rejection.

Applicants submit that the specification provides a sufficient definition for "magnetsome." In particular, the specification defines "magnetosomes" as also being called "ferrosomes" which "refers to an about nanometer-sized magnetite core enwrapped by one or more lipid layers" (specification, page 16, paragraph [0067] in the as-filed application or paragraph [0073] in the published application). Thus, Applicants respectfully request withdrawal of the rejection of claim 61 under 35 U.S.C. § 112.

Rejections Under 35 U.S.C. § 102

A. Claims 58, 59, 61, 63, 67, 69 and 74 were rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,770,222 ("Unger"). Specifically, the Office Action alleges that Unger anticipates the instant invention because Unger teaches preparing cationic liposomal therapeutic systems comprising a bioactive agent with a particle size range between 30 nm to 5 microns that forms a colloidal suspension. Further, the Office Action purports that although Unger does not teach zeta potentials and targeting properties as those instantly claimed, such properties are inherent in the molecules disclosed in Unger. Applicants respectfully traverse the rejection.

The claims of the present application are directed to a method of modifying an agent to enhance its efficacy comprising associating the agent with one or more cationic components to produce a composition having an optimal zeta potential for targeting to an activated vascular site and dispersing the composition in a medium to form colloids having a size of about 10 nm to about 400 nm, wherein the composition has a zeta potential in the range of about +30 mV to +65 mV in about 0.05 mM KCl solution at about pH 7.5. The claims require associating the agent with one or more cationic components to produce a composition having a zeta potential in the range of about +30 mV to +65 mV in about 0.05 mM KCl solution at about pH 7.5 for targeting an activated vascular site and dispersing the composition in a medium to form colloids. The specific range of zeta potential required by the claims targets the composition to the activated vascular site.

For a reference to anticipate the claimed invention, the reference must disclose all the recited steps. Unger does not disclose all the recited steps. Unger does not disclose identifying an optimal range of zeta potential for targeting a composition to an activated endothelial site. Unger discloses various lipids (cols. 7 and 8) including cationic lipids that could be mixed with the therapeutic drug for delivery to a subject. Unger also discloses various ratios of cationic or non-cationic lipids to mix together. However, Unger does not teach the step of obtaining a composition having a zeta potential in the range of +30 mV to +65 mV in about 0.05 mM KCl solution at about pH 7.5 for targeting the composition to an activated vascular site. Unger is not directed to delivering therapeutic drug to activated vascular site. The liposomal compositions obtained by the method of Unger have various zeta potentials for delivery to various sites. The presently claimed invention requires the step of obtaining a composition that has a specific zeta potential that is effective for selective targeting to an activated vascular site.

The Office Action has provided no basis that the method of Unger produces a composition having the range of zeta potential required by the claims and that would be targeted to an activated endothelial site. The Office Action assumes that since Unger describes a cationic liposomal therapeutic system comprising the lipids, DOTAP and DOPC, and particles between 30 nm to 5 microns, the composition would necessarily have the zeta potential and targeting characteristics of the instant invention. Applicants submit that the Office Action has not provided a reasonable basis in fact that the allegedly inherent characteristics necessarily flow from the teachings of the applied prior art. In establishing a *prima facie* case of inherent anticipation, an Examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristics necessary flow from the teachings of the applied prior art (see *Ex parte Levy*, 17 USPQ 2d 1461, 1464 (Bd. Pat. App. Inter. 1990) and MPEP 2112). The lipid composition, particularly the ratios of each lipid impart a specific zeta potential upon the molecule. The claims require that the zeta potential of the composition produced by

the claimed method be in the range of about +30 mV to +65 mV in 0.05 mM KCl solution at a pH of 7.5. In the absence of evidence that the method of Unger produces a composition having the characteristics recited by the claims, Applicants submit that the Examiner has not met his burden of establishing a *prima facie* case of inherency. Accordingly, Applicants respectfully request the reconsideration and withdrawal of the rejection of claims 58-59, 61, 63, 67, 69 and 74 under 35 U.S.C. 102(a).

B. Claims 58, 59, 63, 67, 69 and 74 were rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 6,110,490 ("Thierry"). The Office Action purported that Thierry teaches methods of preparing drug containing liposomes having a size in the range of 200 to 3000 nm wherein specific lipids in the liposomes are cationic and are capable of targeting a therapeutic molecule to a vascular site. Further, the Office Action purports that although Thierry does not teach zeta potentials and targeting properties as those instantly claimed, such properties are inherent in the molecules disclosed in Thierry. Applicants respectfully traverse the rejection.

As discussed above, the claims are directed to modifying an agent to enhance its efficacy comprising associating the agent with one or more cationic components to produce a composition having a zeta potential in the range of about +30 mV to +65 mV in about 0.05 mM KCl solution at about pH 7.5 for targeting an activated vascular site and dispersing the composition in a medium to form colloids having a size of about 10 nm to about 400 nm.

For a reference to anticipate the claimed invention, the reference must disclose the recited steps. Thierry does not disclose the recited steps. Thierry does not disclose identifying an optimal range of zeta potential to target a composition to an activated endothelial site. Thierry discloses various liposomes including cationic and neutral liposomes for combining with nucleic acids. However, Thierry does not teach the step of obtaining a composition having a zeta potential in the range of +30 mV to +65 mV in about 0.05 mM KCl solution at about pH 7.5 for targeting the composition to an activated vascular site. Thierry is not directed to delivering therapeutic drug to activated vascular site. The liposomal compositions obtained by the method of Thierry have various zeta potentials for delivery to various sites. Moreover, Thierry's composition includes a nucleic acid which is negatively charged and would reduce the total zeta potential of the composition. Unlike Thierry, the presently claimed invention requires the step of obtaining a composition that has a specific zeta potential that is effective for selective targeting to an activated vascular site.

The Office Action has provided no basis that the method of Thierry produces a composition having the range of zeta potential required by the claims and that would be specifically targeted to an activated endothelial site. Notably, the Office Action relies on the statement in Thierry that a variety of

cells can be transduced by the liposomes, including vascular endothelial cells (Thierry, column 11, lines 24-30). However, the disclosure is not related to specific targeting, since a variety of cells are transduced (*i.e.* HeLa, NIH-3T3, murine carcinoma, MOLT-3, human macrophages and 293 cells). The method of Thierry is not focused on producing a composition that has a specific zeta potential that targets an activated endothelial site.

The Office Action assumes that since Thierry describes a cationic liposomal therapeutic system comprising the lipid, DOPE, and particles between 200 nm to 3,000 nm, the composition would necessarily have the zeta potential and targeting characteristics of the instant invention. Applicants submit that the Examiner has not provided a reasonable basis in fact that the allegedly inherent characteristics necessarily flow from the teachings of the applied prior art. In establishing a *prima facie* case of inherent anticipation, an Examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristics necessary flow from the teachings of the applied prior art (see *Ex parte Levy*, 17 USPQ 2d 1461, 1464 (Bd. Pat. App. Inter. 1990) and MPEP 2112). However, the lipid composition, particularly the ratios of each lipid impart a specific zeta potential upon the molecule when determined in 0.05 mM KCl soluation at a pH of 7.5. The claims require that the zeta potential of the composition produced by the claimed method be in the range of about +30 mV to +65 mV in 0.05 mM KCl solution at a pH of 7.5. In the absence of evidence that the method of Thierry produces a composition having the characteristics recited by the claims, Applicants submit that the Examiner has not met his burden of establishing a *prima facie* case of inherency. Accordingly, Applicants respectfully request the reconsideration and withdrawal of the rejection of claims 58-59, 63, 67, 69 and 74 under 35 U.S.C. 102(e).

Rejections Under 35 U.S.C. 103(a)

Claim 60 was rejected under 35 U.S.C. 103(a) as being unpatentable over Thierry or Unger. The Office Action admits that both of the above references fail to explicitly state that their employed cationic component comprises molecules having an isoelectric point above 7.5 However, the Office Action purports that cationic lipids by definition must have an isoelectric point above 7, thus absent a showing of unexpected results it would have been obvious to optimize the parameters described by Unger or Thierry by routine experimentation. Applicants respectfully traverse the rejection.

Claim 60 is directed to a method of modifying an agent to enhance its efficacy comprising associating the agent with one or more cationic components to produce a composition having an optimal range of zeta potential and having an isoelectric point above 7.5 for targeting an activated vascular site and dispersing the composition in a medium to form colloids having a size of about 10 nm to about 400

nm. Neither Unger or Thierry disclose the recited steps. Thierry and Unger also do not disclose associating an agent with one or more cationic components to produce a composition having an isoelectric point above 7.5 for targeting an activated vascular site. Moreover, neither Unger or Thierry is directed to selectively targeting an activated vascular site.

Both Unger and Thierry disclose various lipids including cationic and neutral lipids for forming liposomal compositions with therapeutic agents. However, neither Thierry and Unger teach the step of obtaining a composition comprising cationic liposomes and having an optimal zeta potential and an isoelectric point above 7.5 for targeting an activated vascular site.

The Office Action appears to assume that Unger or Thierry inherently disclose the claimed zeta potential and isoelectric point of above 7.5 for targeting the composition to a vascular site (see the Office Action on page 7). Clearly, these references do not state or suggest obtaining a liposomal composition having the instantly claimed zeta potential, isoelectric point, and target specificity.

The present rejection is based on the cited references rendering the claimed invention obvious. It is long and well established that "inherency" and "obviousness" are distinct concepts, which must not to be confused (See *W. L. Gore & Assoc. v. Garlock, Inc.*, 721 F.2d 1540, 1555 (Fed. Cir. 1983)). Applicants respectfully submit that the issue in a consideration of obviousness is not what may or may not be inherent in the cited references, but rather what is known to the ordinary, skilled artisan from those references. As stated in *In re Newell*, 891 F.2d 899 (Fed. Cir. 1989), "[t]hat which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown." *Id.* at 901 (emphasis added); see also *In re Rijckaert*, 9 F.3d 1531, 1535 (Fed. Cir. 1993) (same); *Kloster Speedsteel AB v. Crucible Inc.*, 793 F.2d 1565, 1576 (Fed. Cir. 1986) (holding claims not invalid where defendant failed to show that "inherency would have been obvious to those skilled in the art when invention ... was made"); MPEP § 2141.02.

Applied here, the foregoing authorities make it clear that the property of specific targeting to vascular sites due to a specified zeta potential and isoelectric point, which is not taught by either Unger or Thierry, cannot form the basis of an obviousness rejection. Because the art is devoid of any suggestion that the use of cationic components could be used to specifically target activated vascular sites, Applicants respectfully submit that the rejection for obviousness is not applicable. Accordingly, Applicants respectfully request the reconsideration and withdrawal of the rejection of claim 60 under 35 U.S.C. 103(a).

Conclusion

The foregoing amendments and remarks are being made to place the application in condition for allowance. Applicants respectfully request entry of the amendments, reconsideration and the timely allowance of the pending claims. A favorable action is awaited. Should the Examiner find that an interview would be helpful to further prosecution of this application, they are invited to telephone the undersigned at their convenience.

If there are any additional fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 50-0310. If a fee is required for an extension of time under 37 C.F.R. §1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,
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